Federal Institute for Vaccines and Biomedicines

Paul-Ehrlich-Institut

www.pei.de

Biomarker Regulation

Regulator's perspective

Jan Müller-Berghaus

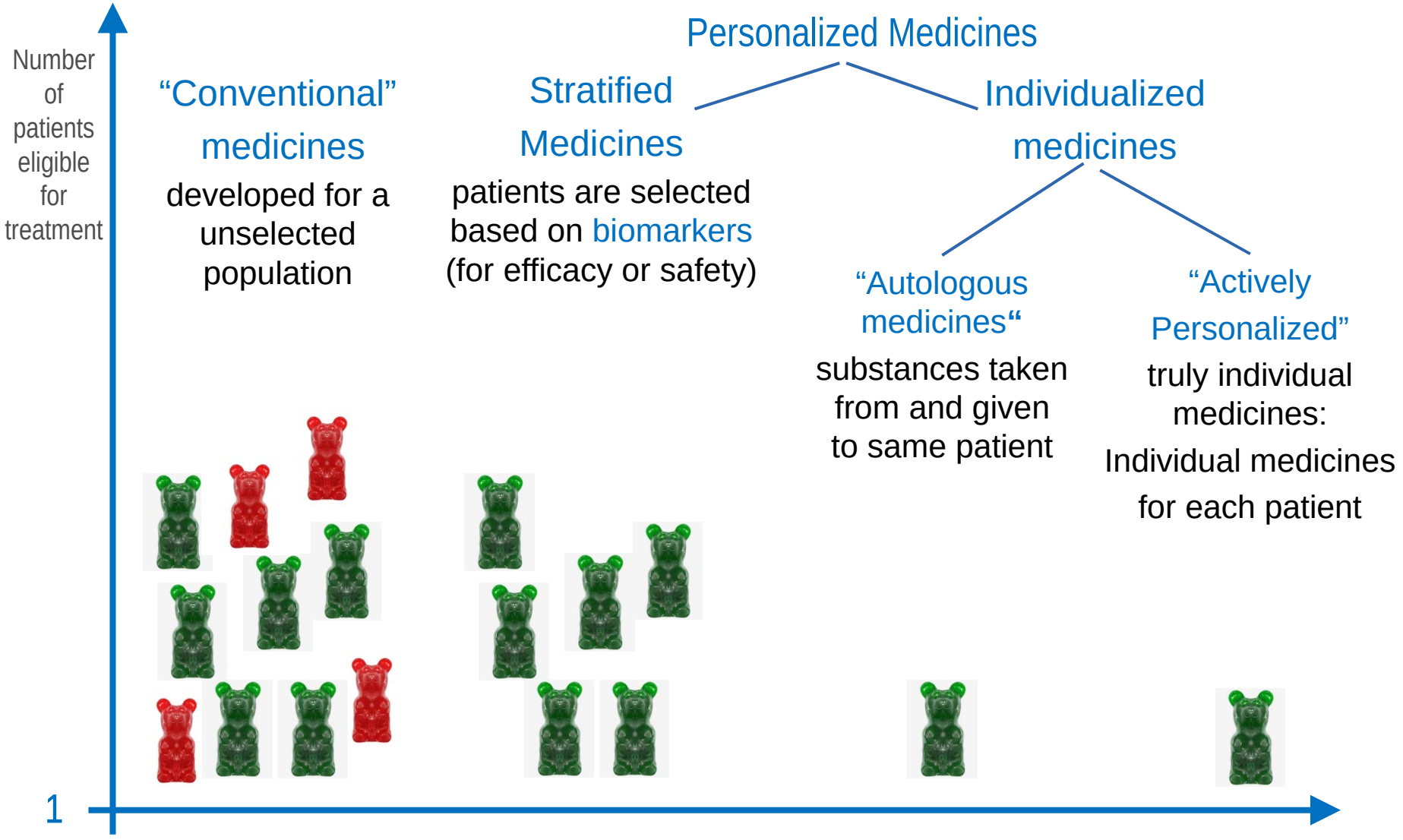
The views presented here are my own and do not necessarily reflect the views of the Paul-Ehrlich-Institut or any other regulatory body

Road map

- **Rationale and types of personalized medicines**

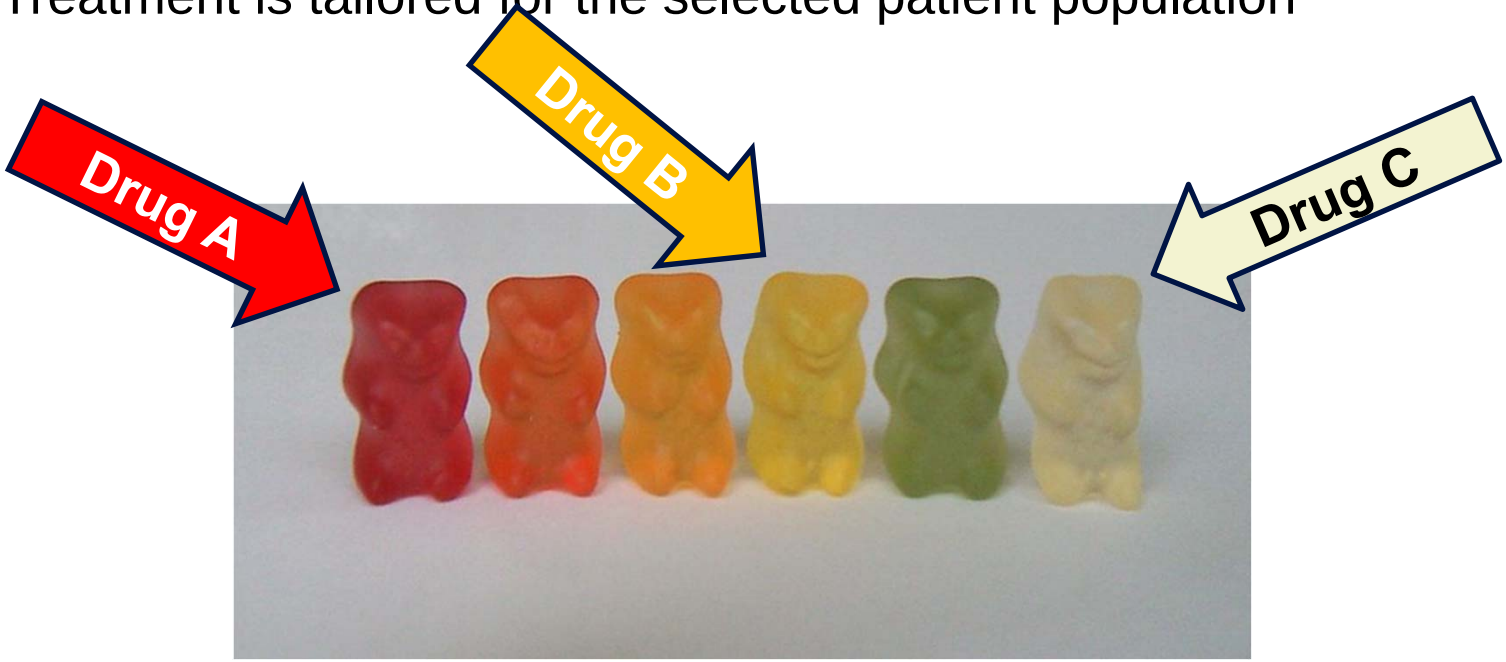
- Pathways for biomarker evaluation and IVD validation

Personalized medicine: a mixed bag of medicines



Stratified medicine: the vision

- Patients are selected based on biomarker (predictive, prognostic)
- Treatment is tailored for the selected patient population



The right drug for the right person at the right dose and at the right time

http://upload.wikimedia.org/wikipedia/commons/thumb/6/66/Gummy_bears.jpg

Biomarker definitions
ICH E15 and FDA definition are similar

- ICH E15: genomic biomarker definition
  - A measurable DNA and/or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other interventions
- FDA (Drug Development Tools Glossary)
  - A biological marker or biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or biological responses to a therapeutic intervention. A biomarker can be a physiologic, pathologic, or anatomic characteristic or measurement that is thought to relate to some aspect of normal or abnormal biologic function or process

- Predictive biomarker: Identifies subpopulation of patients likely to respond to a given therapy or having a better safety profile
- Prognostic biomarker: Identifies patients more likely to have specific course of disease

Stratified authorized medicines in PEI responsibility

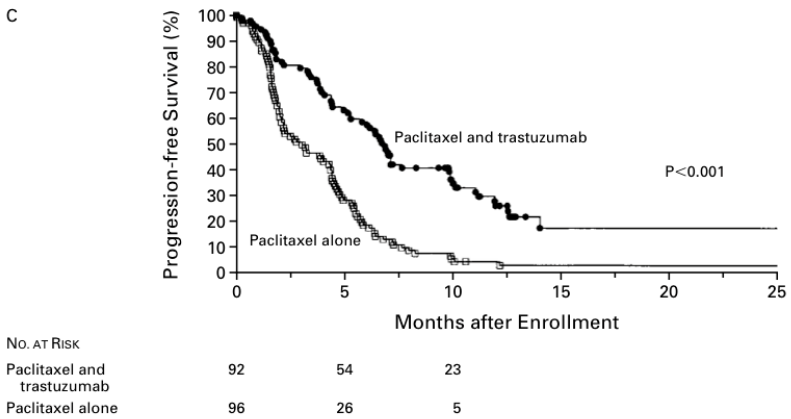
- Monoclonal antibodies (mAb) = approved oncology drugs in PEI responsibility

mAb	Target	Indication	SmPC: Stratifying test
Ofatumumab	CD20 on B cells	CLL	no test mentioned
Cetuximab	EGFR	mCRC, HNSCC	K-RAS^{WT} *(EGFR pos.)*
Trastuzumab	HER2	breast cancer	HER2 pos.
Rituximab	CD20	NHL, CLL, RA	no test mentioned
Catumaxomab	CD3 + EpCAM	malignant ascites	no test mentioned
Panitumumab	EGFR	mCRC	K-RAS^{WT}

- N.B.: target and biomarker of mAb are in most cases identical

Case study: trastuzumab

- **Pivotal trial**: inclusion of HER2 2+ and 3+ breast cancer patients
- Publication: no distinction of results according to expression level, i.e. benefit for the whole population assumed:



- Immunohistochemical classification of HER2 expression based on percentage & intensity of staining (2+/3+ staining detected in > 10% of tumor cells)

Source: N Engl J Med 2001; 344:783

Regulatory assessment

- Safety finding cardiotoxicity
- Regulators requested additional **post-hoc analysis** of clinical trial data
- Retrospective analysis, <u>not result of stratification</u>

Efficacy in HER2 2+ versus HER2 3+ Patients in Combination Therapy: Median (95%CI)

Parameter	**Her2 3+**		**Her2 2+**	
	H+P N=68	**P N=77**	**H+P N=24**	**P N=19**
TTP (months)	7.1 (6.2-12.0)	3.0 (2.0-4.4)	5.3 (3.4-6.6)	2.7 (2.0-5.3)
Survival time (months)*	24.8 (18.6-33.7)	17.9 (11.2-23.8)	16.8 (11.8-25.1)	19.8 (8.1-26.9)
Response rate (%)	49% (36 - 61)	17% (9 - 27)	21% (7 - 42)	16% (3 - 40)

*Cut-off April 99

- Post-hoc analysis
  - not ideal -> higher chance for error in decision making

Resulting IVD description in the SmPC of Herceptin

4.1 Therapeutic indications: Herceptin is indicated for the treatment of patients with metastatic breast cancer whose tumours overexpress **HER2:**

Herceptin should only be used in patients whose tumours have HER2 overexpression at a **3+ level** as determined by immunohistochemistry (see 4.4 Special warnings and special precautions for use and 5.1 Pharmacodynamic properties).

4.2 Posology and method of administration

… HER2 testing is **mandatory** prior to initiation of therapy (see sections 4.4 & 5.1).

4.4 Special warnings and precautions for use

… HER2 testing **must** be performed in a **specialized laboratory** which can **ensure adequate validation** of the testing procedures (see section 5.1).

However: no mentioning of the test used

Stratified medicine: example mAbs

- **Approved mAbs: <u>retrospective analysis</u>, not result of a "true" prospective stratification approach**
  - driven by safety findings or new study data post MA
  - retrospective analysis

  -> higher chance for error in decision making

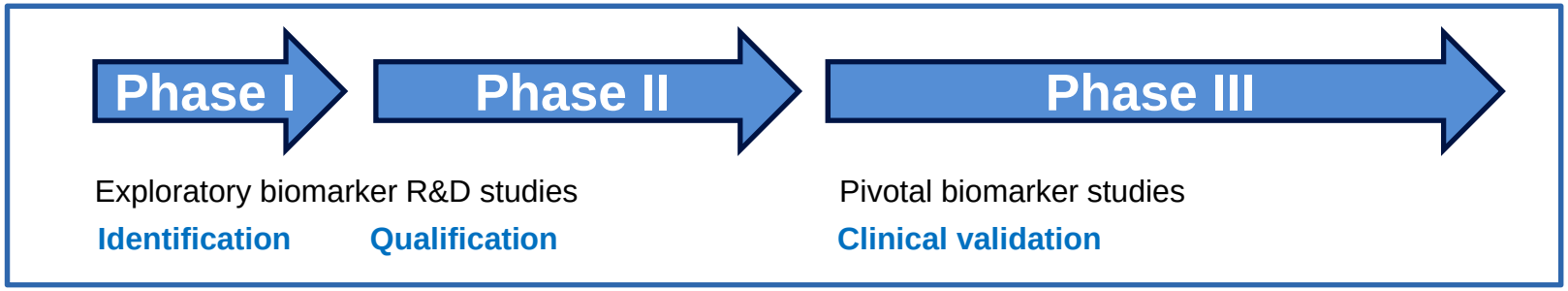
- **Test (IVD) information in SmPC is vague**
  - A mandatory biomarker and its test is fixed, but …
    - only general principle of test (no precise - commercial - assay name)
    - requirements are generally soft: test should be validated and performed in an experienced lab
  - Mention of specific assay used in the <u>pivotal trials</u> could be missing

CAVE! Comparability & quality assurance of the biomarker assay during clinical development (phase I-III /MAA) and whole life cycle of a stratified medicinal product should be demonstrated in the dossier at MAA!

Major Scenarios

- **Dichotomous biomarker**
  - cetuximab for colorectal cancer:
    - selection of patient based on absence of KRAS mutations
- **Semi-quantitative / continuous single biomarker**
  - trastuzumab (Herceptin) for breast cancer:
    - selection of patient based on high expression
- **Combination of biomarkers**
  - Combination of several biomarkers
  - Modelling resulting in complex algorithms without clear mechanistic rationale (e.g. array)
  - The near future?

Ideal clinical biomarker development as part of drug development



- Clear demonstration of **scientific basis** for choice of the marker: Clear MoA
  - Data from non-clinical studies should be supportive of the concept
- **Phase I-II** studies to demonstrate **early** a consistent, reproducible & specific relation of the drug with a claimed effect in a defined subgroup - using an identified marker: Define cut off, technical validation
- Prospective clinical validation of biomarker with drug response / clinical benefit (CAVE! adequate end point) in **phase III**
  - In the overall population
  - Prospectively defined statistical analysis with regard to efficacy and biomarker
- **Assay**: Availability of a (in phase III consistent) testing platform
  - Evaluation for the consequences in clinical practice

Challenges to the development

- Inclusion of „biomarker negative“ patients
  - Gold standard design
    - Include in pivotal trial
    - Analyse with prespecified hypotheses according to prespecified plan, e.g. hierarchical ordering
  - How long can inclusion of „negative“ patients be justified?
    - Is there a clear-cut distinction between positive and negative?
    - What is the disease (e.g. chronic or life-threatening)?
    - What is the potential benefit?
    - How strong is the effect of selection on benefit or risk?
    - Are there other treatment options?

Stratified medicine may result in “Orphanisation“

- Patient populations get smaller because biomarker (prognostic or predictive) defines a subpopulation
- **But** also data set get smaller -> higher uncertainties as regards the evaluation of risk
- More difficult decisions on benefit/risk balance, higher risk of making “wrong” decision for marketing authorisation

- **CAVE!** Committee for orphan medicinal products (COMP) of EMA has granted in **rare cases** **Orphan Drug Designation** based on biomarker-based restriction of population
  - Malignant melanoma: no orphan disease
  - Treatment of HLA-A2, MART-1 positive malignant melanoma: orphan disease

Road map

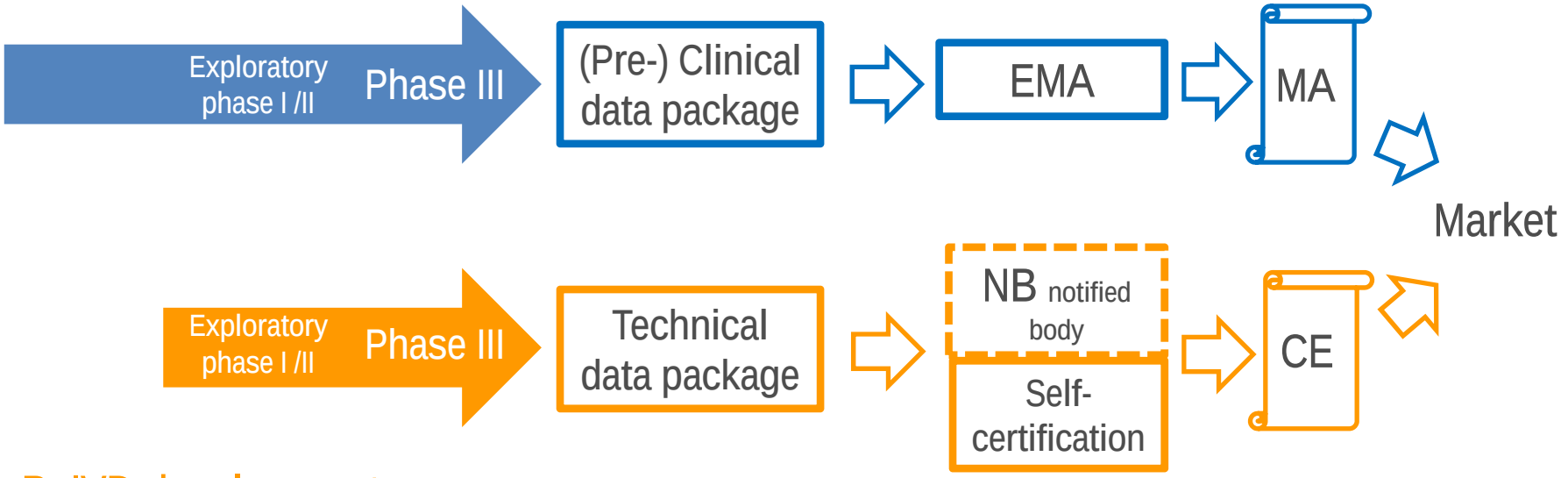
- Rationale and types of personalized medicines

- **Pathways for biomarker evaluation and IVD validation**

EU: Biomarker evaluation is different from In-Vitro Diagnostics (IVD) validation

A. Biomarker development

Biomarker evaluation as part of clinical drug development



B. IVD development

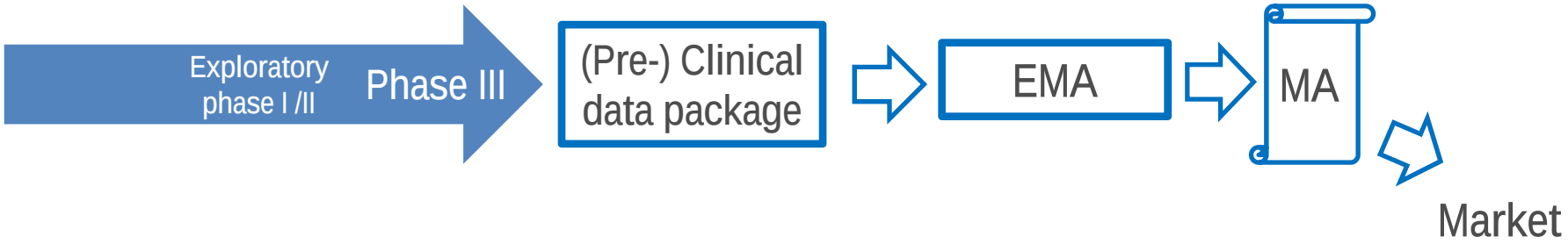
Technical validation

C. In-House tests

Biomarker “approval” pathway: Clinical drug development includes Biomarker evaluation

A. Biomarker development

Biomarker evaluation as part of clinical drug development



B. IVD development

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EMA guidance is focused on pharmacogenomic biomarkers

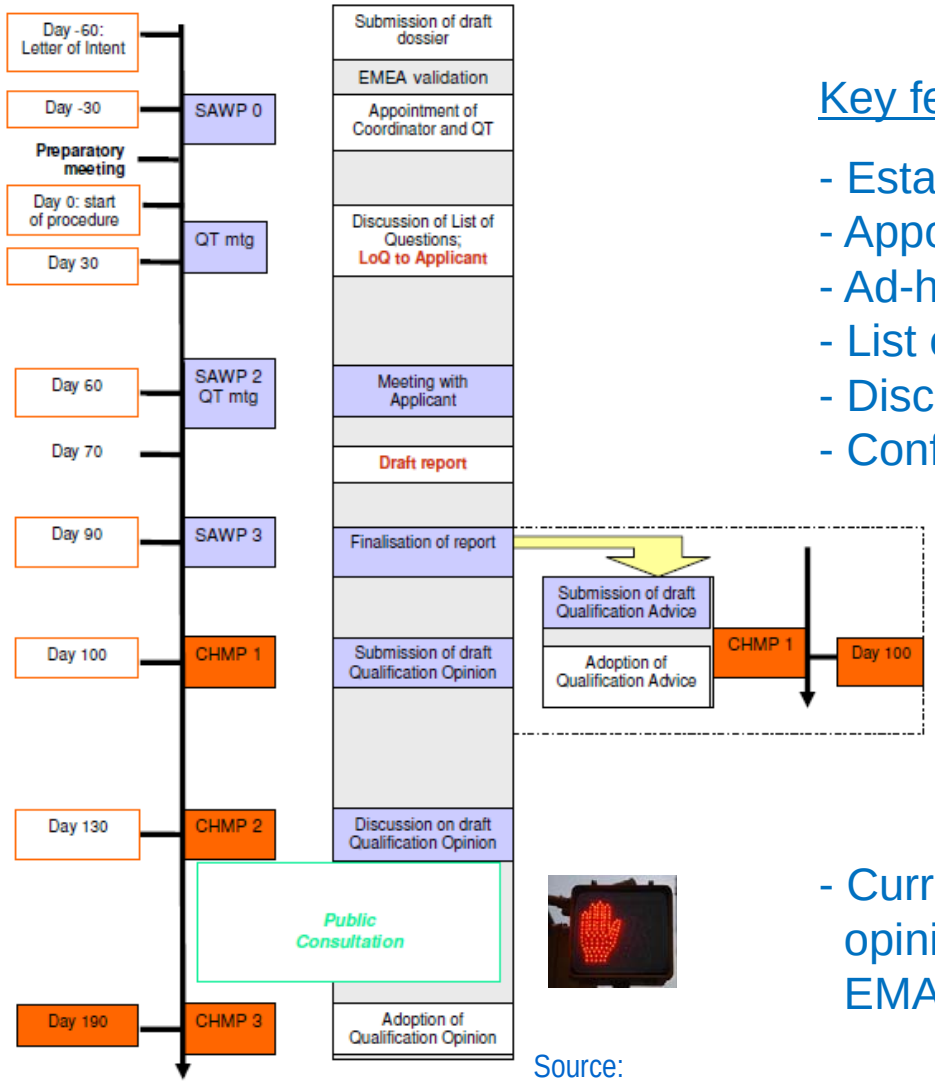
Topic	Documents	Reference number	Publication date	Effective date	Remarks
Reflection paper on co-development of pharmacogenomic biomarkers and assays in the context of drug development	Draft guideline	EMA/CHMP /641298/2008	Released for consultation July 2010		Deadline for comments November 2010
Reflection paper on methodological issues with pharmacogenomic biomarkers in relation to clinical development and patient selection	Draft guideline	EMA/CHMP /446337/2011	Released for consultation July 2010		Deadline for comments 25 November 2011
Reflection paper on pharmacogenomics in oncology	Draft guideline	CHMP/PGxWP/128435/06	Released for consultation April 2008		Deadline for comments July 2008
International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Topic E15 definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories	Adopted guideline Draft guideline	CHMP/ICH /437986/06	November 2007	May 2008	
Reflection paper on pharmacogenomic samples, testing and data handling	Overview of comments Adopted guideline	EMEA/CHMP /PGxWP /201914/06	November 2007	November 2007	

www.ema.europa.eu Home>Regulatory>Human medicines>Scientific guidelines>Multidisciplinary >Pharmacogenomics

Biomarker development is part of drug development
EMA scientific support: Qualification of novel methodologies

- **New voluntary EMA initiative**: scientific advice to support qualification of innovative development methods in the context of R&D
  - » Primarily (initially) intended for biomarker (tests)
- Contrary to “standard” scientific advice: Scientific data will be evaluated
- Two pathways:
  - CHMP qualification opinions (public)
    - » opinion on the acceptability of novel biomarkers
    - » method can apply to non-clinical or to clinical studies
      - most applicable and helpful for consortiums
  - CHMP qualification advice (confidential)
    - » advice on protocols and methods that are intended to develop a novel biomarker with the aim of moving towards qualification.
      - most applicable and helpful for developers

EMA scientific qualification support



Source:
EMA/CHMP/SAWP/72894/2008 Rev.1

Key features:

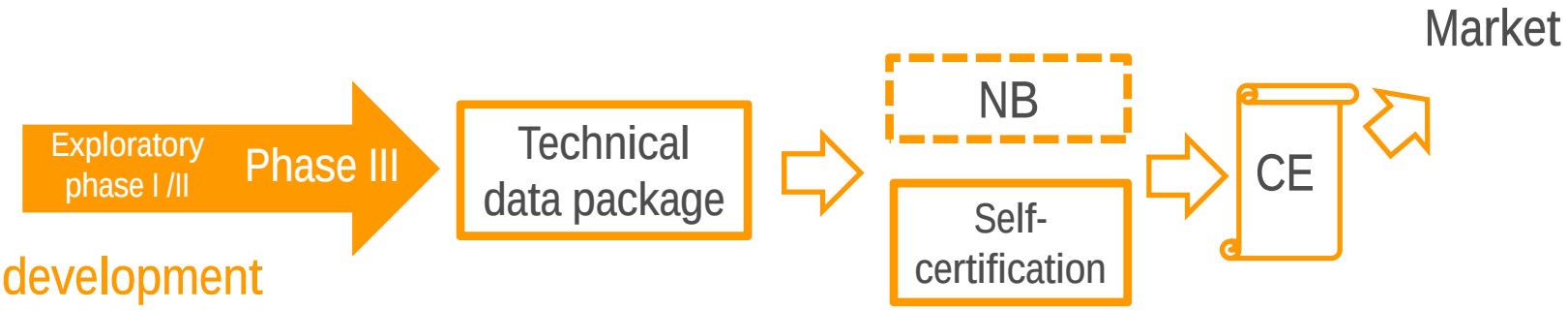
- Established procedure
- Appointment of a coordinator
- Ad-hoc qualification team
- List of Question (LoQ)
- Discussion of LoQ with developer
- Confidential advice or public opinion

- Currently four biomarker qualification opinions adopted and published on EMA homepage

The IVD Pathway

A. Biomarker development

Biomarker evaluation as part of clinical drug development



B. IVD development

Technical validation

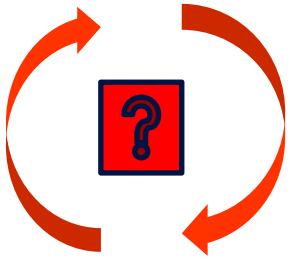
C. In-House tests

Regulatory environment: IVD medical devices
Currently an IVD is developed independently

- If produced by a **commercial IVD manufacturer** diagnostics are subject to Directive 98/79/EC on In-Vitro-Diagnostic Medical Devices (Oct. 1998)
  - Essential requirements of Directive 98/79/EC apply
  - Classification under Annex III of the Directive
    - → self-certification by the IVD manufacturer → CE label
  - No involvement of a third party (Notified Body, NB), no independent control
- If developed as an **in-house test** by a **non-commercial IVD manufacturer**
  - Essential requirements of DIRECTIVE 98/79/EC do not apply
  - Heterogeneous regulation of in house tests in Europe

Towards a companion diagnostics pathway?

Biomarker Pathway



IVD Pathway

A different approach:
FDA draft guidance on companion diagnostics

- Definition of a companion diagnostic acc. to FDA:

  An IVD companion diagnostic device could be essential for the safe and effective use of a corresponding therapeutic product to:

  - …identify patients who are most likely to benefit from a particular therapeutic product
  - … identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product
  - …

- If a drug depends on a companion IVD for it to be safe and effective then the test must to be approved too
  - **-> Drug and corresponding test are assessed and approved together**

- Example for recent FDA approval
  - Detection of ALK-positive NSCLC **using an FDA-approved test**, **indicated for this use**, is necessary for selection of patients for treatment with XALKORI

Actual regulatory challenges for the development of an IVD - intended for a predictive biomarker - in the FDA sense of a “companion diagnostic“

- Should at least **stricter requirements** (i.e. similar as for list B IVD) be applied for biomarkers used in stratified medicine?
- Is the assessment of **performance evaluation** of an IVD only possible with a clear knowledge and understanding of the pivotal trial data?
  - Possible risk for the patient
    - Not receiving a treatment that would be beneficial
    - Receiving a treatment that would not be beneficial, but harmful
- Should regulators be involved in the assessment of IVD data in context of marketing authorisation?
  - -> Linking of clinical and technical validation data!
- Revision of IVD Directive 98/79/EC?
  - Demonstration of clinical utility of combination of medicinal product and IVD in the context of MA -> should be part of the overall benefit/risk assessment

Directive 98/79/EC is currently under revision
Draft Oct. 2012

- **General revisions**
  - Improvement of NB's power: unannounced audits; lab & sample controls
  - Risk based approach following the *Global Harmonization Task Force Model*: class A (lowest risk) up class D (highest risk)
  - Vigilance & market surveillance: Trend notification, periodic summary reports
  - EU reference labs

- **Revisions specific for IVD: On the way to a "companion IVD"**
  - Definition and classification of **companion IVD** to **risk class C**
  - Class C: Mandatory proof of concept by Notified Body (NB)
    - Commercial IVD developer should present to NB:
      - Demonstration of suitability of the companion IVD for the drug
      - Summary of safety & clinical performance, incl. study results
      - Proposed SPC and PIL
  - Closer connection between NB and Regulatory Agency (EMA; nat. agencies)
    - EMA should be involved in IVD assessment

Directive 98/79/EC currently under revision - draft Oct.12
On the way to a “companion IVD”

Currently: Independent not overlapping pathways -> Biomarker + IVD
Proposed: Linking of NB & Regulatory Authority -> Towards a companion IVD

A. Biomarker development

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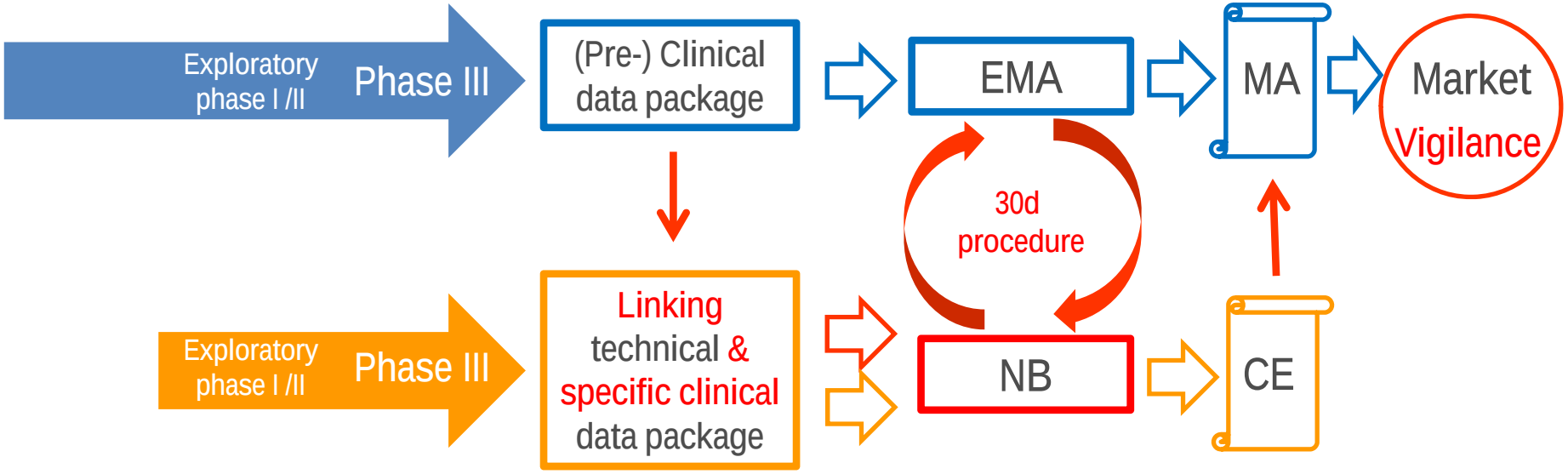
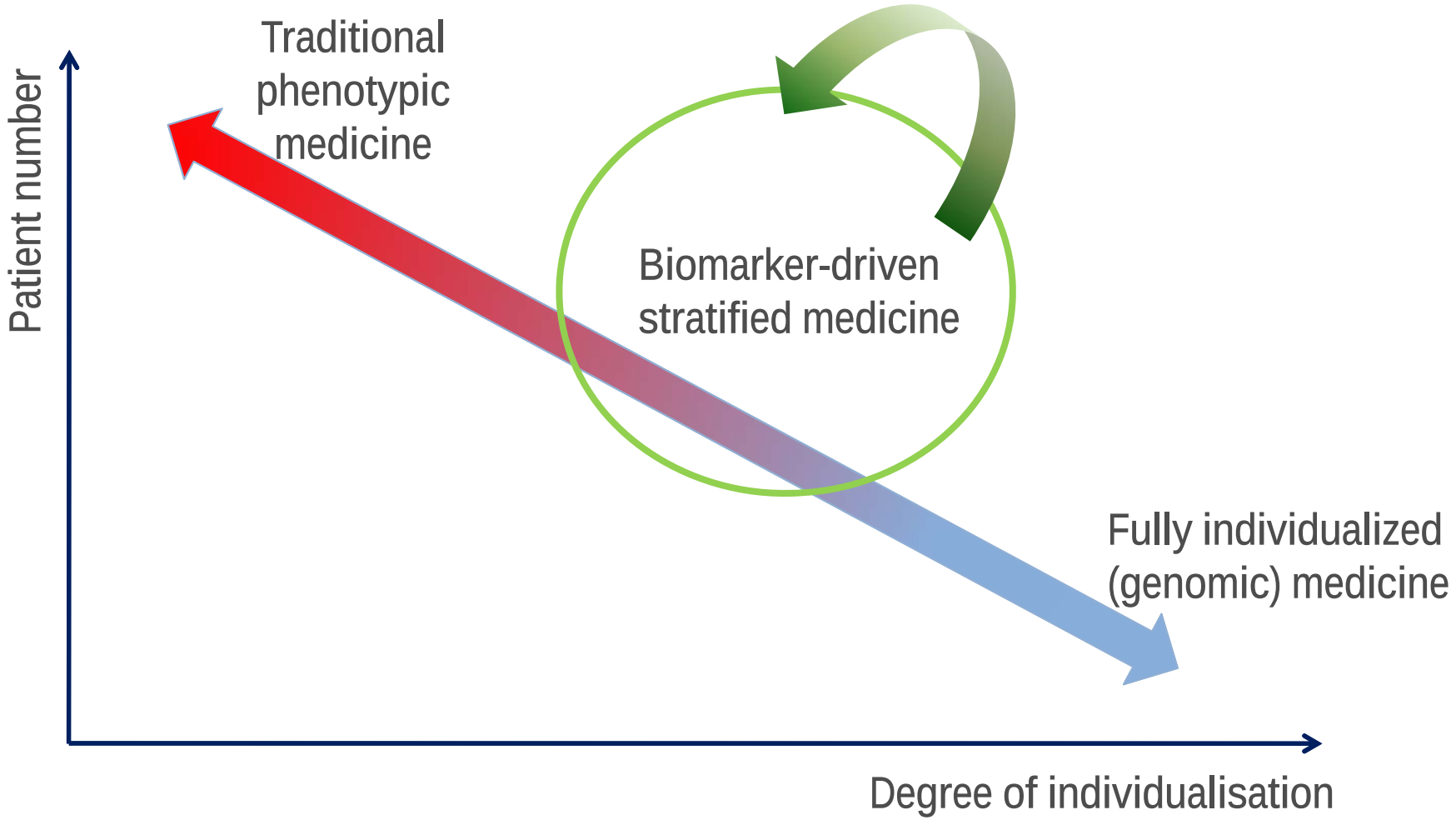


B. Companion IVD development

Technical validation & clinical evaluation

C. In-House tests

Where we are and future developments



Research, assessment and licensing of safe and efficacious biomedicines

Ehrlich in seinem Arbeitszimmer